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Role of Umbilical Cord Mesenchymal Derived Exosomes in Diseases

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Abstract: Stem cells are divided into embryonic stem cells and adult stem cells. Mesenchymal stem cells (MSCs) are one of the most important adult stem cells. These cells possess characteristic plastic adhesion properties, the ability to differentiate into osteoblasts, chondrocytes and adipocytes in vitro, are positive for CD73, CD90 and CD105, major histocompatibility complex class II, and negative for CD11b, CD14, CD31, CD34 and CD45. MSCS can be isolated from different sources, such as umbilical cord, umbilical cord blood, bone marrow (BM), adipose tissue, cervical tissue, placenta, skeletal muscle tissue, liver tissue, dental pulp, synovium, saphenous vein, lung and dermal tissue and periodontal ligament. They have many abilities, such as the ability to differentiate, expand in vitro, produce nutrients and regulate immunity. Therefore, bone marrow mesenchymal stem cells can help in tissue repair and treatment, such as diabetes, cardiovascular diseases, diseases of the liver, lung, kidney, nervous system, and other systems, and of course, bone. As a noninvasive method, there is no ethical issues, low immunogenicity, self-renewal ability faster, more stable, doubling time proliferation ability is higher, compared with other sources, the treatment of human umbilical cord MSC is based on cells and regenerative medicine preferred candidates. However, hucMscs have relative limitations in maintaining biological activity, quantifying bioactive substances, and clinical therapeutic logistics. Therefore, it seems necessary to find a cell-free method with the same output and efficacy. Exosomes are one of the members of extracellular vesicles, and due to their many biological activities and cell communication, they have attracted the attention of researchers as a new strategy for cell-based cell-free therapies. In the study of HUCMSCexo, all the advantages of HUCMSC, such as the therapeutic factor transfer of low immunogenicity HUCMSC, the prominent self-renewal and immunomodulatory properties have been reported to be conserved. In addition, no tumorigenic outcome was found in these studies. Therefore, this article reviews the application of HUCMSC-EXO in different diseases.

Keywords: Stem cells; Mesenchymal stem cells; Umbilical cord; Exosomes

1. Kidney disease

HUCMSC-EXO was found to be beneficial in the treatment of cisplatin-induced renal toxicity. Cisplatin (DDP) is an anticancer drug that can induce renal tubular epithelial cell apoptosis through oxidative stress. However, treatment with HUCMSC-EXO reduced creatinine levels, urea nitrogen proximal tubular necrosis, apoptosis, cisplatin-induced oxidative stress, and the formation of a large number of renal tubular protein models in vivo. In addition, in vitro treatment with HUCMSC-EXO also reduced oxidative stress, the number of apoptotic cells and p38 mitogen-activated protein kinase activation pathway, followed by an increase in caspase-3 expression and cell proliferation in NRK-52E cells. It is reported that autophagy plays an important role in mitigating tissue damage. Pretreatment with HUCMSC-EXO induces autophagy activation by reducing the expression of phosphorylated mammalian target of rapamycin and autophagy-related genes and autophagy marker proteins in NRK-52E cells. It also reduced cell apoptosis and inflammatory response. MTOR is an evolutionarily conserved nutrition-sensing serine/threonine protein kinase. Therefore, HUCMSCEXO may be considered as a therapeutic strategy to prevent the side effects of cisplatin.

2. Eye disease

Idiopathic macular hole is one of the causes of visual impairment. Vitrectomy is the main treatment for MH. For seven patients with large refractory MH, intravitreal injection of HUCMSC and hucMSC-Exos with heavy silicone oil and 20%SF6 or 14%C3F8 tamponade was performed after standard PPV combined with internal limiting membrane peeling. Six patients with MH were closed, and 1 patient remained flat and open. The best corrected visual acuity improved in 5 patients with MH closure. One patient with MH closure and a 4-year history of MH did not observe any change in BCVA. In patients treated with MSC, fibrous membranes were observed on the retina. Inflammatory responses have also been reported in patients receiving high doses of MSCs-EXO. This study demonstrates that intravitreal injection of MSC-

exO and MSC at the end of regular PPV can improve the anatomical and visual outcomes of refractory MH surgery. The main limitation of this study is the lack of a control group. Retinal damage caused by infection and ischemia can lead to irreversible visual impairment. Currently, there is no neuroprotective therapy for retinal damage. Although several therapeutic approaches, such as stem cell transplantation and 7, 8-dihydroxyflavonoids, Nmethy-aspartate receptor antagonists, Ca2+ channel blockers, and anti-inflammatory drugs, are used to improve retinal cell function, these approaches have not been accepted for clinical treatment. Previous studies have shown that intravenous injection of MSCs can inhibit apoptosis and inflammatory response in retinal laser injury.

3. Alzheimer's disease

Alzheimer's disease is one of the most common neurodegenerative disorders that cause cognitive and memory impairment. Amyloid-β peptides induce neuroinflammatory processes in the central nervous system in AD, and excessive Aβ accumulation has been observed. In one study, the effects of HUCMSC-EXO were investigated in AβPP/PS1 transgenic AD mouse model and BV2 cells. The accumulation and formation of Aβ plaques can activate microglia as A major component of neuroimmunomodulation. Microglia, similar to macrophages, have two completely different functional activation states. In the pro-inflammatory activated state, microglia cause neurodegenerative diseases by increasing pro-inflammatory cytokines such as TNF-α and IL-1β, leading to Aβ accumulation and reducing Aβ clearance. Microglia in the other state cause A neuroprotective effect by increasing anti-inflammatory cytokines, leading to improved inflammation and increased Aβ clearance. In addition, these cytokines cause a return to tissue homeostasis, alleviating the proinflammatory immune response and wound healing. Autophagy is the physiological degradation of organelles and proteins that can be increased by proinflammatory cytokines. Inflammation induces autophagy in peripheral blood mononuclear cells (PBMC).

4. Spinal cord injury

M1 macrophages can produce inflammatory cytokines, such as IL-6, TNF-α and IL-1β, which damage host cells. In fact, M2 macrophages suppress the inflammatory immune response by producing IL-4 and IL-10 cytokines, which increase angiogenesis and eliminate necrotic components. Studies have shown that HUC-MSC-EXO for the treatment of spinal cord injury induces M1 to M2 phenotype polarization and improved performance. This polarization also reduced the production of inflammatory cytokines such as IFN-γ, IL-6, TNF-α and macrophage inflammatory protein-1α.

5. Ductal adenocarcinoma of the pancreas

MiR-145-5p5p, a class of tumor suppressives, was found to be down-regulated in a variety of cancers, including pancreatic ductal adenocarcinoma, hepatocellular carcinoma, colorectal cancer, gastric cancer and breast cancer. Ding's study showed that HUCMSC-EXOs could affect the delivery of miR-145-5p, prevent PDAC invasion, induce cell apoptosis, and lead to low expression of Smad3. Moreover, in vivo results showed that the growth of xenograft tumors was reduced after miR-145-5p overexpression in mice.

6. Liver disease

Liver fibrosis is caused by chronic injuries such as viral hepatitis and alcohol and drug use. Liver transplantation is the ultimate treatment for the disease. However, due to the limited number of donors and the high mortality rate of patients with liver fibrosis, it is essential to find alternative treatments. HUCMSC-EXO was used to treat carbon tetrachloride-induced liver fibrosis in mice. The results showed that the fibroblasts were derived from hepatocytes and underwent epithelial-mesenchymal transition and collagen synthesis. Various studies have also shown that after phosphorylation, Smad3 and Smad2 form a complex with Smad4 and then translocate to the nucleus to regulate the transcription of target genes responsible for EMT such as collagen I, Snail and Smad7. In addition, TGF-B1 activates the Smad2/3 pathway and leads to EMT. Transplantation of HUCMSC-EXO also caused the down-regulation of TGF-B1 and the consequent inhibition of Smad2 phosphorylation and the reversal of EMT in vivo. Treatment of human liver cell line HL7702 with HUCMSC-EXO also caused EMT in vitro, reversing the expression of EMT-related markers and spindle-shaped cells. In addition, HUCMSC-EXO improved serum aspartate aminotransferase activity and reduced TGF-B1, Smad2 phosphorylation and collagen types I and III in vivo.

7. Skin wound healing

Previous studies have shown that MSC-EXO plays a key role in tissue repair. However, the role of MSC-EXO in skin wound healing has not been investigated. Wnt/ β-catenin signaling plays an important role in wound healing. HUCMSC-EXO could significantly reduce cell apoptosis by activating AKT signaling pathway in a rat model of skin burn injury. As mentioned above, MSC-EXO increased tissue regeneration. However, it is not clear how MSC-EXO controls stem cell expansion following the regenerative response to prevent overcrowding and poor growth. In the current study, they examined the ability of HUCMSC-EXO to regulate collagen expression and stem cell expansion in a rat deep second-degree burn model. The results showed that HUCMSC-EXO treatment promoted the self-regulation of Wnt/ β-catenin signal-

ing in the stage of skin regeneration and remodeling, prevented collagen deposition, and increased cell expansion at week 4 after transplantation. Under high cell density conditions, 14-3-3ζ appeared in HUCMSC-EXO, leading to the formation of an inhibition/complex that resulted in the phosphorylation of YAP in Ser127. Studies have shown that YAP and p-LATS form a complex and 14-3-3ζ is required for the formation of this complex to activate the Hippo pathway. 14-3-3ζ transfer also leads to p-LATS accumulation. High cell density thus represents the condition for activation of Hippo-YAP signaling, and hucMSC-Exo-mediated 14-3-3ζ delivery ensures sufficient levels of p-LATS to phosphorylate YAP. These findings suggest that HUCMSC-EXO not only acts as an "accelerator" of Wnt/ β-catenin signaling to restore damaged skin tissue, but also as a signaling pathway to orchestrate controlled skin regeneration through YAP regulation.

8. Closing Remarks

At present, mesenchymal stem cells (MSCS) are widely used. For example, tissue repair or disease treatment and so on. However, there are many limitations in the application of hucMscs, such as maintenance of biological activity, quantification of active substances, and so on. Therefore, it is particularly important to find a treatment that is not interfered by cells. Exosomes are derived from a variety of sources, such as hucMscs, and are involved in cell communication. Therefore, exosomes can replace cell-based therapies.

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